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Review Article

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A Review of Active Surveillance of Papillary Thyroid Microcarcinoma

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ABSTRACT

The incidence of papillary thyroid carcinoma (PTC) has increased remarkably over the past few decades. Given the indolent nature of PTC, active surveillance (AS) has been suggested as an alternative management option to immediate surgery in the management of low-risk papillary thyroid microcarcinoma (PTMC). While there is conflicting evidence regarding potential risk factors for disease progression, many groups have demonstrated the efficacy and safety of AS and proposed risk stratification, which can help to select appropriate patients. This review aims to summarize the data regarding low-risk PTMC as well as important considerations of AS.

Keywords: Thyroid cancer; Papillary; Active surveillance

INTRODUCTION

The incidence of papillary thyroid carcinoma (PTC) has increased remarkably over the past few decades. In Korea, there has been a rapid rise in the number of thyroid cancer diagnoses, and currently, Korea's thyroid cancer incidence rate is the highest in the world. The incidence of thyroid cancer in Korea increased from 7.2 per 100,000 persons in 1999 to 55.8 per 100,000 persons in 2018 (1), and this been mirrored in many countries around the world, including the United States, several European countries, and England (2,3). The rising incidence of thyroid cancer has been attributed in large part to the increased utilization of high-resolution ultrasound and technical advances coupled with formal population screening programs (4-7).

Before the controversy, once diagnosed, PTC patients received active treatment, as with patients with other malignant tumors. Increases in PTC incidence rates without associated changes in mortality rates have been considered evidence for PTC overdiagnosis or overtreatment (8). This can be attributed to the fact that most PTC cases diagnosed incidentally by imaging area are papillary thyroid microcarcinomas (PTMCs) defined by a diameter of 1 cm of less (T1aN0M0 disease). Following thyroid surgery for PTMC, disease-specific mortality rates, loco-regional recurrence rates, and distant recurrence rates have been reported to be <1%, 2%–6%, and 1%–2%, respectively. These excellent outcomes are more related to the indolent nature of the disease than the effectiveness of treatment (9).

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After receiving media attention for its increasing incidence in Korea in 2014, PTC dropped from the most commonly diagnosed type of cancer to the third most commonly diagnosed type of cancer in 2015 in Korea (10). However, it became the most commonly diagnosed type of cancer in Korea again in 2019 according to an unpublished press release from the Korea Central Cancer Registry.

These days, many patients want to receive a detailed and updated explanation of observation and surgery protocols for the treatment of their thyroid cancer and to choose a treatment method based on this knowledge. This review aims to summarize the data regarding low-risk PTMC as well as important considerations of AS.

ACTIVE SURVEILLANCE (AS) OF PTC

AS is a treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are changes in test results that show the condition is getting worse. Representatively, research on AS in thyroid cancer and prostate cancer is actively underway (11).

The AS strategy for low-risk papillary microcarcinoma (PTMC) was first proposed by Dr. Akira Miyauchi at Kuma Hospital in 1993 (12). AS was adopted as a management modality for PTMC in guidelines issued by the Japan Association of Endocrine Surgeons/Japanese Society of Thyroid Surgery in 2011 and those of the American Thyroid Association in 2015 (9,13).

1. Inclusion and exclusion criteria

Low-risk PTMC patients were selected as candidates for the AS trial at Kuma Hospital, and other studies suggested proper inclusion and exclusion criteria (14,15). The criteria for inclusion were tumor size ≤1 cm, no macroscopic invasion onto the perithyroidal soft tissue, no cervical lymph node involvement, absence of high-risk location (tumor adjacent to the trachea or recurrent laryngeal nerve), and no aggressive variant of PTMC by fine-needle aspiration cytology or core-needle biopsy (12). Tuttle et al. (15) in the United States selected intrathyroidal tumors ≤1.5 cm as the observation object. Potential contraindications for the application of AS are high-risk surgical candidates, patients with concurrent malignancy, and patients with other medical conditions that require treatment prior to surgical intervention for thyroid disease. Sawka et al. (16) reported a pan-Canadian AS protocol as a tumor size of <2 cm, and they excluded those pregnant at the time of study enrollment. Oh et al. (17) in Korea excluded patients (i) who decided against AS after a detailed discussion with the attending physician comparing surgical intervention and AS, (ii) with other underlying malignancies, (iii) with a high risk of general anesthesia complications due to a cardiopulmonary problem, (iv) with uncontrolled systemic comorbidities, or (v) who were pregnant.

2. Follow-up protocol for AS

Surveillance is employed in the form of ultrasound, and it is generally performed every 6 months for the first year and then annually. Signs of significant disease progression indicating a need for surgical intervention of delayed thyroid surgery, as established by Kuma Hospital, include an increase in the maximum tumor diameter on ultrasound by ≥3 mm or the development of locoregional or distant metastasis (18). Additionally, more dynamic characterization of tumor growth based on 3-D volume measurements may allow for earlier determination of whether a PTC is stable or growing (15).

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3. Results of AS for low-risk PTMC

In 2003, the first report of the use of AS for a small number of low-risk PTMCs at Kuma Hospital was published. Ito et al. (14) proposed observation without surgical treatment as a treatment option for a total of 732 patients diagnosed with PTMC from 1993 to 2001. Of these, 162 patients chose observation, and the other 570 patients chose surgical treatment with a mean follow-up duration of 48.7 months. The study's analysis revealed that in the over 5-year follow-up period, in the observation group, 27.5% of patients showed a 2mm or more increase in tumor size (maximum diameter), 60.3% were unchanged, and 12.1% showed a 2 mm or more decrease in tumor size on ultrasonography. Moreover, the tumor exceeded 10 mm in 10.2% of patients, and lymph node metastasis in the lateral compartments was detected in 1.2% of patients. In the surgical treatment group, lymph node metastasis was confirmed in 50.5% of patients, tumor multiplicity was seen in 42.8% of patients, and the rate of recurrence was 2.7% at 5 years and 5.0% at 8 years after surgery. The authors of this study concluded that patients can choose observation while their tumors are not progressing, although they are pathologically multifocal and involve lymph nodes in high incidence (14).

In 2014, Ito et al. (19) reported on 1,235 patients with low-risk PTMC according to patient age (young, <40 years: middle-aged, 40–59 years: old, ≥60 years). After a 10-year follow-up, the rates of tumor-size enlargement and the novel appearance of node metastasis were 8.0% and 3.8%, respectively. In the young age group, the rate of tumor size enlargement was 12.1% (vs. 4.0% in the old age group), that of the novel appearance of node metastasis was 16.1% (vs. 0.5% in the old age group), and that of the progression to clinical disease was 22.5% (vs. 2.5% in the old age group). They concluded that old patients with subclinical low-risk PTMC may be the best candidates for observation. Although PTMC in young patients may be more progressive than that in older patients, it might not be too late to perform surgery after subclinical PTMC has progressed to clinical disease, regardless of patient age.

A Korean study described tumor progression in 14% of 192 patients with a median tumor diameter of 5.5mm within an observation period of 30 months. In the tumor progression group, 85% showed a tumor volume increase of >50% without a maximum diameter increase of ≥3 mm. A total of 13% underwent delayed thyroid surgery at a median of 31.2 months, and among the surgical treatment patients, 29% had cervical lymph node metastasis on pathologic examination. There were no significant risk factors associated with increased tumor size, such as age, sex, or Hashimoto thyroiditis. They concluded that some PTMCs could grow significantly after a relatively short period of AS. We also found that the change in tumor volume was more sensitive for detecting tumor progression than the change in the maximum tumor diameter (20).

Another Korean multicenter study enrolled 370 PTMC patients with a median follow-up of 32.5 months. During the study, 86 (23.2%) patients were found to have an increase in tumor volume, and 13 (3.5%) patients showed an increase in the maximum diameter of the tumor. The cumulative incidence of volume increase gradually rose with time (6.9%, 17.3%, 28.2%, and 36.2% after 2, 3, 4, and 5 years, respectively). The risk of volume increase in patients <45 years of age was twice that in older patients (P=0.002). During the period, 58 (15.7%) patients underwent delayed thyroid surgery due to anxiety (37.9%), tumor size increase (32.8%), or the appearance of cervical lymph node metastasis (8.6%). Lymph node metastasis was found in 29.3% of patients on pathological examination. The authors concluded that tumor volume change is a more sensitive means of evaluating tumor growth and that AS can be carefully applied to select patients and more cautiously to younger patients.

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To examine another aspect of AS, Oh et al. (21) analyzed 273 patients who underwent AS for more than 1 year and were divided into two groups: rapid-growing (tumor volume doubling time [TVDT] <5 years) and stable (TVDT ≥5 years). Over a median of 42 months (29–61 months) of AS, a total of 28.2% of patients had a TVDT of less than 5 years, and these patients were classified as being at high risk for tumor progression. Of them, 10.3% had a TVDT of less than 2 years, 5.1% had a TVDT between 2 and 3 years, 6.2% had a TVDT between 3 and 4 years, 6.6% had a TVDT between 4 and 5 years, and 71.8% had a TVDT of 5 years or more. Patients in the rapid-growing group (28.2%) were significantly younger (P=0.004) than those in the stable group (71.8%). Being younger than 50 years of age was significantly associated with rapid tumor growth of PTC (odds ratio [OR], 2.31; confidence interval [CI], 1.30–4.31; P=0.004) in the multivariate analysis. In the ultrasound findings, macrocalficiation was independently associated with the rapid tumor growth of PTCs (OR, 4.98; CI, 2.19–11.69; P<0.001). They concluded that determination of TVDT during the early phase of AS may be helpful in predicting rapidly progressing PTCs and deciding whether to adopt an early surgical approach (21).

The first American study on AS with 291 patients was published in 2017 by Tuttle et al. (15) Over a median AS of 25 (6–166) months, growth in tumor diameter of 3mm or more was observed in 3.8% patients, with a cumulative incidence of 2.5% (2 years) and 12.1% (5 years). No regional or distant metastases developed during AS. In the multivariable analysis, both younger age at diagnosis (hazard ratio [HR] per year, 0.92; 95% CI, 0.87–0.98; P=0.006) and risk category at presentation (HR for inappropriate, 55.17; 95% CI, 9.4–323.19; P<0.001) were independently associated with the likelihood of tumor growth. Of the tumors experiencing volume growth, kinetics demonstrated a classic exponential growth pattern, with a median doubling time of 2.2 years (range, 0.5–4.8 years; median $r^2 = 0.75$; range, 0.42–0.99). The authors concluded that serial measurement of tumor volumes may facilitate early identification of tumors that will continue to grow and thereby inform the timing of surveillance imaging and therapeutic interventions (15).

OTHER CONSIDERATIONS DURING AS

1. Tumor growth in AS

Most studies measure the tumor diameter as an indicator of the tumor progression in an ultrasound test (a maximum diameter increase of ≥3 mm compared with the baseline size) (6,12,14). However, some studies suggest that determination of the 3-D volume is a more sensitive marker of PTMC growth. Of interest, more patients show volume enlargement than maximum diameter enlargement (15,20,21). When making a decision regarding surgical intervention during the AS period, TVDT is considered a strong dynamic marker for the prediction of the growth rate and progression of the thyroid cancer. Evidence is limited, and which indicator is better for monitoring tumor progression remains unknown.

2. Role of serum thyroid-stimulating hormone (TSH) in AS

TSH suppression is a common strategy to avoid the recurrence of the progression of a recurred lesion of differentiated thyroid carcinoma, including PTC. However current guidelines do not support routine TSH suppression for patients with low-risk PTMC after surgery, because it may induce osteoporosis, especially in elderly female patients (9). One retrospective study reported that the serum TSH value was not related to the progression of low-risk PTC during observation (22). TSH suppression is controversial in patients who

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choose AS. However, in a Japanese study, a small number of patients (4%) were treated with TSH suppression during AS because of the physician's preference, and all but one patient demonstrated clinically stable disease (19). Further studies are needed to draw any confirmative conclusions on TSH suppression.

3. BRAF and telomerase reverse transcriptase (TERT) mutations in AS

Recently, molecular marker-based risk stratification of thyroid cancer has been proposed to better estimate the cancer risk. In Korea, more than 80% of PTC cases harbor the BRAF mutation. Although the BRAF mutation has drawn much attention based on their high prevalence, their association with recurrence or mortality is unclear (23). Some large multicenter studies have reported an association of the BRAF mutation with high recurrence and mortality rates (24,25). However, many studies from East Asian countries, including Korea, Taiwan, and Japan, have demonstrated that the BRAF mutation is not associated with disease-free survival or poor prognostic factors (26-28). Many physicians wonder why thyroid cancer-related mortality is still low, although the BRAF mutation is highly prevalent. These findings suggest that the isolated BRAF mutation may be a sensitive but not specific marker of tumor recurrence and tumor-related mortality (23). The TERT promoter mutation has been identified in thyroid cancer, and it allows cancer cells to immortalize. It was found in 10%–20% of differentiated thyroid carcinomas and 40% of dedifferentiated thyroid carcinomas. It is highly prevalent in patients of old age and in those with large tumors, aggressive histologies, advanced stages, and distant metastases. Lee et al. (29) reported that the identification of the TERT promoter mutation in preoperative fine-needle aspiration biopsy (FNAB) helped to better characterize the prognosis and the triage of PTC patients in Korea, where a large proportion of PTCs showed the BRAF mutation (29). Although there are some potential markers that may predict mild progression activity of PTC, these are insufficient to preclude the AS approach to low-risk PTMC.

4. Cost of AS versus surgery

With the increasing incidence of PTC, the increasing medical costs for the diagnosis and treatment of PTC have presented a social issue. Lubitz et al. (30) warned that the societal medical costs for thyroid cancer treatment of US$1.6 billion in 2013 might increase to US$3.5 billion by 2030. Medical costs are also a great concern for individual patients. To obtain evidence on the cumulative economic costs of AS, several parameters should be included in an analysis, including repeat neck ultrasonography, repeat FNAB, calculated quality-adjusted life year, surgical costs and complications, medications, and surgery for recurrence. Ventatesh et al. (31) in the USA conducted a theoretical cost analysis and concluded that the cost-effectiveness of hemithyroidectomy for PTMC is dependent largely on the health utility associated with the AS of individual patients as well as the remaining life expectancy of the patient after diagnosis. Moreover, Chan et al. (32) in Hong Kong used a similar model and concluded that AS was cost saving up to 16 years from diagnosis and remained cost-effective from 17 years onward. An Australian study demonstrated that the surgery may have a long-term economic advantage for younger Australian patients with PTMC who are likely to require more than 16.2 years of follow-up in an AS scheme (33). As medical costs and insurance systems vary greatly across countries, the cost-effectiveness of AS versus surgery should be evaluated in each country.

5. Quality of life (QQL) of AS versus surgery

The main consideration of AS is the oncologic outcomes. However, it is also important to consider any impact on health-related QOL. QOL assessment can demonstrate subjective

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symptoms associated with the disease itself or the side effects of treatment as well as the real clinical benefits of the treatment for patients (34). Jeon et al. (35) performed a cross-sectional study of QOL comparing an AS group (43 patients) with a lobectomy (LB) group (148 patients). The scores on a short-form health survey questionnaire were compared. The groups differed significantly in terms of emotional problems, and the thyroid cancer-specific QOL questionnaire also showed a statistically significant difference between the groups with respect to three scores: neuromuscular, throat/mouth, and scar problems. They concluded that the LB group experienced more health-related problems than those managed by AS (35). Another multicenter prospective cohort study on the QOL of patients treated with AS versus immediate surgery enrolled 203 patients in the AS group and 192 patients in the surgery group with a median follow-up of 8 months. They concluded that the QOL of PTMC patients differed according to the type of treatment. Moreover, the AS group exhibited better psychological health at baseline and better physical and psychological health at follow-up than the surgery group. However, a study with a longer follow-up period is needed to draw a confirmative conclusion (36).

6. Other therapeutic strategies for low-risk PTMC

Some studies have explored therapeutic strategies for low-risk PTMC other than AS or immediate surgery. Radiofrequency ablation (RFA) for differentiated thyroid carcinoma has been performed on persons (i) with previous surgery for whom repeat surgery was higher risk because of risks associated with reoperation, (ii) who were poor surgical candidates, (iii) who refused surgery due to unexplained reasons, and (iv) who had PTMC and were candidates for AS (37). However, its efficacy as a treatment options for low-risk PTMC has been debatable. Studies have shown the efficacy of RFA when used for PTMC. Zhang et al. (38) reported that 94 patients post-RFA were followed for 64.2 months, and 93 (98.9%) showed no recurrence. In addition, they experienced better QOL, did not have to use levothyroxine, and enjoyed reduced costs compared to surgery (38). Contrary to this, some clinicians have claimed that thermal ablation may lead to incomplete treatment. Ma et al. (39) reported three PTMC cases who were treated with RFA and later underwent surgery showing histological evidence of residual tumors. Although RFA is a relatively safe technique, complications include thermal injury and/or compression from hemorrhage of the recurrent laryngeal nerve of the vagus nerve, skin burns, and pain at the site of the procedure. In addition, treating the primary lesion with RFA might result in the loss of a biomarker of the disease. Further studies are needed to produce evidence of another treatment option for low-risk PTMC.

DISCUSSION

In Korea, PTC received media attention in 2014 due to its increasing incidence and the controversy over overtreatment and overdiagnosis (8). Many doctors were concerned about the PTMC treatment policy (immediate surgery vs. AS). Just a few years ago, the available data on the outcome of AS for low-risk PTMC were mostly from Japan (18). However, further data on various populations from different countries with diverse cultures, dietary habits, and attitudes have now been collected (40). It is well known that the prognosis of PTMC is better than that of other cancer entities. Thus, the paradigm of an aggressive approach has shifted toward a more conservative treatment protocol. Current evidence supports the development and promotion of AS, but several limitations are cause for concern. First, despite the accumulation of various studies, most have been performed in East Asia. As such, whether their conclusions can be generalized to other populations remains unknown.

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Second, the possibility of subjective bias cannot be excluded. It is important to keep in mind that most patients who enrolled in the AS studies had highly selected, low-risk tumors with favorable cytologic and ultrasound features. Additionally, the various studies have not revealed the tumor progression rate over 10 years. Third, despite the absence of accurate methods to distinguish stable PTMC from aggressive PTMC, AS strategies have been used by most clinicians. Identifying biomarkers would help in the decision-making process. Finally, clinicians should address the psychological changes and mental state of the patient when considering the management strategies.

With sufficient clinical data, doctors should give low-risk PTMC patients proper information, discuss proper treatment options with them, and respect their choices. They should introduce the advantages and disadvantages of AS and surgery, and carefully draw patients' attention to both. After the decision making, doctors should conduct standardized AS or surgery protocol.

CONCLUSION

AS has been verified as a safe and reasonable approach for appropriately selected patients with low-risk PTMC. However, ongoing further study to optimize patient selection, surveillance protocols, and improved implementation across practices are needed. Further, additional assessment of companion risk assessment tools is also needed and will require thorough long-term prospective study.

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